MICROWAVE-PROMOTED CONVERSION OF HETEROCYCLIC AMINES TO CORRESPONDING AMIDES UNDER SOLVENT-FREE CONDITIONS

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Abstract : An array of heterocyclic amides was synthesized efficiently by combining corresponding amines and benzoyl chloride in one-pot under microwave irradiation. The reaction times were shorter, yields were higher. What is more, the regioselectivity was excellent, which made the protocol support us an entry to selective protection of diverse amino groups.

Key Words : microwave-promoted, solvent-free, heterocyclic amide, benzoyl chloride

Introduction

The relatively stable amide bond is not only common in natural-occurring materials (e.g., peptides and proteins) but is also found in many synthetic substances.[1,2] This makes the amide function important to synthetic chemists, especially in peptide[1] and lactam[2] syntheses, in which the formation of amide bonds is crucial. Many methods for the synthesis of carboxamides exist. In general, amides are formed from carboxylic acids and amines in the presence of coupling reagents[3] or accomplished by the reaction of acyl chlorides and amines in solvent.[4] Although good results are obtained with both approaches, they are time consuming and associated with difficult separation and lower yields. To improve efficiency mild methods for preparation of amides in the absence of

coupling reagents and solvent are highly desired.

In the last decade, microwaves (MWs) have been used to simplify and improve reaction conditions for many classic organic reactions. Reactions performed under MW-conditions proceed faster, more cleanly, and in much better yields than similar reactions under conventional conditions.[5-9] In connection with solvent-free conditions, MW methods result in efficient and safe technology, 'Green Chemistry'.[5,10] The MW-assisted synthesis of amides has already been investigated.[11-14] However, in these studies a limited number of amines and carboxylic acids were combined to afforded the corresponding amides. The compliance of MW-conditions with heterocyclic amine present in the inputs was almost not examined. Furthermore, because of the lower activity of carboxylic acids, some reactions between amines and carboxylic acids achieved very low conversions even after long reaction times. Therefore, there is still a great demand for a method using acyl chlorides for the synthesis of amides.

Results and Discussion

In view of the limitation of the existing methods, here, we wish to report an improved protocol for synthesis of amides (Scheme-1)

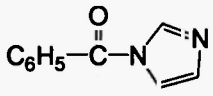
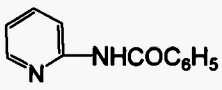
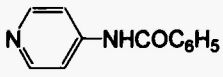
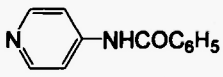
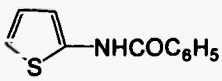
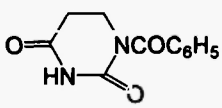
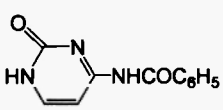
Scheme-1

from benzoyl chloride and diverse heterocyclic amines by microwave irradiation under solvent-free conditions, which considerably broadens the scope of amide synthesis. With microwave heating, the experimental conditions were carefully monitored (by TLC) to regulate the ratio of the substrates , irradiation time and power level of the microwave oven to achieve the maximum yield. A 1:1 mol ratio of benzoyl chloride to heterocyclic amines and 250W were the most appropriate reaction conditions for the synthesis of

N-benzoyl imidazole, 2-benzamidopyridine, 4-benzamidopyridine, 2-benzamidopyrimidine and 2-benzamidothiazole in view of reaction times and yields. In general, the reaction times were shorter (1-3 min), and the yields were good (80-92%).

When Adenine, Uracil and Cytosine were added into benzoyl chloride, keeping the reaction conditions the same, the conversions to corresponding amides were very low. So we tried to change the reaction conditions. A 1:2 mol ratio of amines to benzoyl chloride and 495W were the optimal conditions for synthesis of the above compounds. Under the reaction conditions, the yields increased dramaticly even though a little amine was detected. It is noteworthy that in the end only obtained N^6-benzoyladenine, N^1-benzoyluracil and N^4-benzoylcytosine respectively, and that their by-products N^9-benzoyladenine, N^3-benzoyluracil and N^1-benzoylcytosine were not detected (monitored by TLC), the result was consistent with the merit of microwave heating : selectivity. To some extent, it supported us a method for selective protection of the amino group. When we used 4-aminoantipyrine and o-phthalimide as starting materials, keeping the reaction conditions the same, no products were observed with despite the change of the power level and the mol ratio. The possible reason: 4-aminoantipyrine hardly dissolve in the benzoyl chloride, which make it not react with benzoyl chloride. When referred to o-phthalimide, it is possible that the two carbonyl groups scatter the electron charge density of nitrogen atom and further lead to the reaction proceed difficultly. The result was reported in Table-1.

Table-1. Microwave-promoted synthesis of heterocyclic amide under solvent-free conditions[a]

Entry	Substrate	Product	Power (W)	Time (min)	Yield[b] (%)	M.P. (Lit:) (°C)
1	Imidazole		250	1.5	80	Liquid (19-20)[15a]
2	2-Aminopyridine		250	2	92	84-87 (85-87)[15b]
3	4-Aminopyridine		250	1	94	207-210 (211)[15c]
4	2-Aminopyrimidine		250	3	82	140-142 (142)[15d]
5[c]	Adenine		495	5	81	240-243 (242-243)[15e]
6	2-Aminothiazole		250	1	91	150-151 (151)[15d]
7[c]	O-phthalimide	____	495	30	0	____
8[c]	4-Amino-antipyrine	____	495	30	0	____-
9[c]	Uracil		495	8	63	165-168 (167-168.5)[15f]
10[c]	Cytosine		495	10	58	347-349 (350)[12g]

[a] All the products were reported previously in the literature and fully characterized by m.p. ,IR, ^{1}H NMR.

[b] Isolated yields.

[c] The reaction was performed at a 1: 2 mol ratio of amine to benzoyl chloride.

Conclusion

254 -promoted solvent-free synthesis of heterocyclic amides by direct assembly of amines and benzoyl chloride under neutral conditions is a versatile method for the efficient synthesis of amides. A set of structurally heterocyclic amides were obtained under optimized conditions. This method supported us an entry to selective protecting diverse amino groups. Furthermore, it is superior from the view of yield, reaction time, selectivity and simple manipulation to the reported methods. All the merits make this protocol potentially a powerful tool for peptide synthesis.

Experimental

Melting points were uncorrected. IR spectra were recorded on a FTS-40 spectrophotometer in KBr. ^{1}H NMR were measured on a Bruker DPX-400M spectrometer using TMS as internal standard.

A typical procedure for preparation of 2-benzamidopyrimidine:

2-Aminopyrimidine (2mmol, 190mg) and benzoyl chloride (2mmol, 280mg) were mixed thoroughly in a crucible and exposed to the domestic microwave oven at 250W for 3min under solvent-free conditions. After the reaction was completed (monitored by TLC), the powder was obtained, and the crude product was recrystallized in 95% alcohol and parched, then the pure product was obtained.

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